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Further Evidence Suggesting the Presence of a Locus, on Human Chromosome 5q31-q33, Influencing the Intensity of Infection with *Schistosoma mansoni*

To the Editor:

Recently, Marquet et al. (1996) described a linkage study of the susceptibility to intestinal schistosomiasis, one of the most important worm infestations in humans. The individuals included in that study mostly showed a low-susceptibility phenotype, and a major gene (*SM1*) controlling the intensity of infection was found (Abel et al. 1991). Now, *SM1* has been localized to chromosome 5q31-q33 (Marquet et al. 1996). The study area was a hyperendemic schistosomiasis focus (infection with *Schistosoma mansoni*) in Brazil (Dessein et al. 1988).

We conducted a study in a newly emerged, epidemic focus of intestinal schistosomiasis, in northern Senegal, where the human population has been shown to be heavily infected with *S. mansoni,* as measured by the numbers of excreted worm eggs and the circulating antigen levels (Stelma et al. 1993). Recruitment, epidemiological study design, and parasitological methods have been described in detail elsewhere (Stelma et al. 1993). A total of 154 subjects were included. They belonged to 15 extended pedigrees, which contained 33 nuclear families. The distribution of logarithmically transformed egg counts ($\log_{10}$[egg count + 1]) is shown in figure 1. By use of the procedure described by Abel et al. (1991), the egg counts, after having been logarithmically transformed ($\log_{10}$[egg count + 1]), were adjusted for sex, age, and exposure, as estimated by water-contact measurements.

The resulting values differ, in distribution, from those calculated for the population in the Brazilian focus, in which a minority of individuals formed a distinct subgroup with relatively high egg counts (Abel et al. 1991). The Senegalese subjects, who have been exposed for no longer than 7 years (Stelma et al. 1993), present with a more balanced distribution of infection intensities, and no such subgroup is discernible. Complex segregation analysis of the nuclear families was performed, by use of complete selection as the mode of ascertainment and by use of the POINTER program (Lalouel and Morton 1981; Morton et al. 1983). The analysis revealed additional differences between the two populations. In Brazil, the familial distribution of phenotypes corresponded well to the Mendelian segregation of a codominant major gene (Abel et al. 1991). For the Senegalese sample, models of codominant (degree of dominance d = .96, displacement t = 2.09, and allele frequency q = .47), dominant (d = 1, t = 2.04, and q = .46), or recessive (d = 0, t = 0.89, and q = .16) modes of inheritance all were rejected ($P < .005$, in all cases); however, nontransmission of a major gene (d = .55, t = 3.03, and q = .97; transmission probability [τ] of $\tau 1 = \tau 2 = \tau 3$ = .22) was not rejected ($P > .14$). All the P values mentioned above are given for comparison with a general non-Mendelian model. A mixed Mendelian codominant model (d = 1, t = 2.07, q = .45, and heritability H in children = .03) does not have a significantly higher likelihood than a Mendelian codominant model without a multifactorial component (d = .96, t = 2.09, and q = .47); the corresponding P value for this comparison is .69. When the mixed Mendelian codominant model is compared with models allowing for non-Mendelian transmission probabilities, both the models assuming equal transmission probabilities and those allowing for free estimates of the transmission probabilities clearly have higher likelihoods ($P < .005$, in both cases) than the mixed Mendelian codominant model.

When a dominant mode of inheritance was assumed—which, as determined from the results of the segregation analysis, was the best-fitting model for our data—no significant LOD score was obtained by use of FASTLINK 2.0 (maximum LOD score of 0.322, with

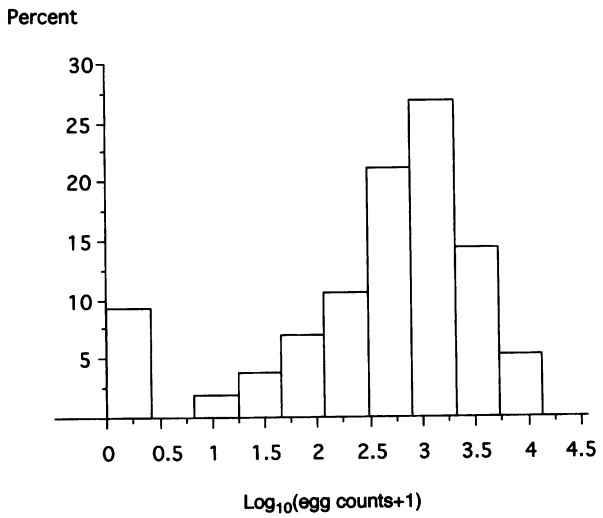

Figure 1 Distribution of egg counts, as $\log_{10}$(egg count + 1), among 154 Senegalese subjects recently exposed to *S. mansoni* transmission

marker *D5S410*) (Lathrop and Lalouel 1984; Lathrop et al. 1984, 1986; Schaffer et al. 1994; Schaffer, in press). In contrast, methods that are independent of the specification of the genotype-phenotype relationship confirmed the effect and the location of *SM1*. The weighted pairwise correlation (WPC) test (version 2.0), a nonparametric method for use with general pedigrees (Commenges 1994; Commenges et al. 1994; Commenges and Abel 1996), yielded *P* values of .005 and .002 for the marker loci *D5S636* and *D5S410*, respectively (table 1). A multipoint analysis of sib pairs (MAPMAKER/SIBS, version 2.0) (Kruglyak and Lander 1995), used as an alternative nonparametric approach, resulted in a maximum *Z* score (standard normal variate) of 2.01, which corresponded to a *P* value of .022 (fig. 2). These two methods differ in that, for a given marker, the WPC test, using extended pedigrees, will eliminate from the analysis pedigrees with no information for that marker, whereas MAPMAKER/SIBS uses data for nuclear families only, thereby losing some of the information contained in the more extended pedigrees. Nevertheless, both methods reached their highest levels of significance close to marker *D5S410*, located on the more distal border of the interval for *SM1*, described by Marquet et al. (1996).

The failure of conventional LOD-score analysis to yield a significant result may be due to the differences between the two populations. These differences may be due to various reasons. First, *SM1* (i.e., the major gene) may be effective late in the course of schistosomiasis, so that its effect is being missed in the short-term-exposed Senegalese group. Second, in the Senegalese sample, the allele frequency of *SM1* may be too low to be detected, since the overall gene frequencies may differ between the two populations. This might relate to any environmental factors—for instance, other infectious diseases, such as malaria, that are prevalent in the Senegalese study area but not in the Brazilian study area. Third, schistosomiasis itself may be the cause for different gene frequencies in the two study groups: In the Brazilian population, long-term exposure may have resulted in selection for the major-gene effect, contributing to the evolution of a low-susceptibility phenotype, which has not yet evolved in the short-term-exposed Senegalese population. Whatever the reason may be, the absence of a major-gene effect, which may be due to the factors mentioned above, may reflect a more complex genetic model. This may be why conventional LOD-score analysis was not successful in the confirmation of the position of *SM1*, in the Senegalese population (Clerget-Darpoux et al. 1986).

In conclusion, these data present a successful replication of the recent finding of a locus on chromosome 5, termed "*SM1*," that influences the intensity of infection with *S. mansoni*. The data suggesting the existence of

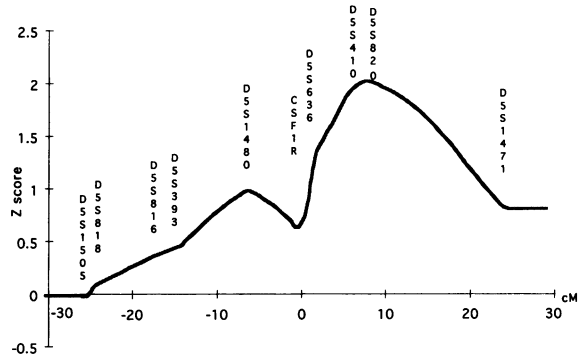

Figure 2 Results of nonparametric multipoint analysis for sib pairs infected with *S. mansoni*, by use of standardized residuals of adjusted egg counts as quantitative phenotypes. MAPMAKER/SIBS was used with the Haldane mapping function and with the first-pairs scoring function. The *Z* scores obtained are standard normal variates (Kruglyak and Lander 1995). They showed a maximum *Z* score of 2.01, corresponding to a *P* value of .022. The markers included were *D5S1505, D5S818, D5S816, D5S393, D5S1480, CSF1R, D5S636, D5S410, D5S820,* and *D5S1471*. Genotypes were determined by use of an automated sequencer (model 373A; Applied Biosystems) and the GENOTYPER software. Marker allele frequencies were estimated from those of the founders in the pedigrees. The horizontal axis represents the genetic distance, in centimorgans, with the position of CSF1R chosen as the origin, in accordance with the study by Marquet et al. (1996)

Table 1

Results of the Nonparametric WPC Test

Marker	Intermarker Distance[a] (cM)	WPC-OP Score[b]	*P* Value
D5S1505	−25.4	1.284	.100
D5S818	−23.3	.647	.259
D5S816	−15.8	.767	.222
D5S393	−14.5	.741	.229
D5S1480	−6.5	1.536	.062
CSF1R	0	2.190	.014
D5S636	1.5	2.563	.005
D5S410	5.5	2.864	.002
D5S820	8.2	1.766	.039
D5S1471	23.4	1.146	.126

NOTE.—Standardized residuals of adjusted egg counts were used as the quantitative phenotype. Genotypes were determined with an automated sequencer (model 373A; Applied Biosystems) and the GENOTYPER software.

[a] Based on the data from the study by Marquet et al. (1996) and on the comprehensive human linkage map (Cooperative Human Linkage Center 1994). The position of CSF1R was chosen as the origin, in accordance with the study by Marquet et al. (1996).

[b] The WPC statistic based on ordinary residuals and permutation inference. The WPC-OP score, like the *Z* score, follows a standard normal distribution (Commenges 1994; Commenges et al. 1994; Commenges and Abel 1996).

differences between populations, possibly owing to a selective pressure of *S. mansoni* infection, may motivate further studies.

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Multiple Sclerosis in Sardinia Is Associated and in Linkage Disequilibrium with HLA-DR3 and -DR4 Alleles

To the Editor:

The preponderance of genetic factors in attempts to account for susceptibility to multiple sclerosis (MS), a common inflammatory and demyelinating disease of young adults, has recently been demonstrated (Ebers et al. 1995). The inheritance of MS appears to be complex and is believed to involve several genes (Ebers et al. 1996; The Multiple Sclerosis Genetics Group 1996; Sawcer et al. 1996). Methodological approaches to the study of genes conferring susceptibility to MS include association studies, which measure the frequency of a specific allele in affected and healthy populations, and linkage studies, which trace the inheritance of a gene from parents and correlate these genes to disease susceptibility. The genetic approach to MS has preferentially been performed on genes involved in immune mechanisms—in particular, on HLA genes (Haegert and Marrosu 1994). Association studies have established a link between the disease and the HLA class II DRB1*1501-DQA1*0102-DQB1*0602 haplotype (the serologically defined DR2,DQw1 allele [Bodmer et al. 1995]) in Caucasian MS patients (Hillert and Olerup 1993). Nevertheless,